Combined Injury: Radiation in Combination with Trauma, Infectious Disease, or Chemical Exposures

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ABSTRACT

Biomedical consequences of radiation exposure are exacerbated by concurrent trauma and/or disease. After a nuclear detonation burns and/or wounds in combination with radiation are highly likely. At Hiroshima and Nagasaki, 60% to 70% of radiation victims sustained traumatic injury. In the 1986 Chernobyl reactor incident, 10% of the 237 accident victims received both significant radiation doses and burns. Animal studies in several species demonstrate that traumatic injuries increase mortality associated with acute radiation syndrome. For example, Brooks et al. [Brooks 1952], found that combining 1 Gy radiation (12% mortality alone) with a modest sized thermal burn (non-lethal alone) elicited 75% mortality in a canine model. Similarly, in rats a burn associated with 50% mortality inflicted in conjunction with sublethal radiation (2.5 Gy) increased mortality to 95% [Alpen 1954]. Burns and wounds shift the radiation dose response curve to the left. In a study of gamma-irradiated mice, the LD_{50} with radiation alone decreased from 9.63 Gy with radiation alone to 8.20 Gy with a non-lethal, 15% body surface burn and to 7.61 Gy with a non-lethal, 15% body surface wound. Although the mechanisms of this interaction are undetermined, increased susceptibility to infection is known to contribute to the synergism. Infectious disease is a likely confounder following a nuclear event that can disrupt public health infrastructure. In combination with radiation, morbidity and mortality from infection will increase significantly. An infectious agent can be naturally occurring in the environment or it can be intentionally dispersed as a biological warfare agent. Because radiation impairs the immune response and compromises the normal barriers to infection (i.e., the epithelial cell layers of the intestinal tract and lung), an individual becomes more susceptible to pathogens. When radiation injury is combined with exposure to highly infectious pathogens, fewer microbes are needed to establish an infection and the clinical manifestations are more severe, as demonstrated in animal studies. For example, when sublethally irradiated mice (7 Gy) were challenged with a sublethal dose of Klebsiella pneumoniae (5% mortality in non-irradiated animals), all of the mice died. Even at radiation doses as low as 0.5 Gy, mortality from K. pneumoniae was increased [Whitnall 2000]. In addition, latent infections, such as Herpes or scrub typhus, can become active after radiation. Accepted preventative and treatment strategies can be inadequate when host defenses have been compromised by exposure to radiation. Use of live attenuated organisms for immunization may actually cause the manifestation of the disease if given after irradiation. Concurrent chemical exposures may also occur with a nuclear event, either by release from local factories or storage facilities or by intentional dispersal. Although less is known about the physiological interactions of chemicals with radiation, there are sufficient data suggesting that interactions will exacerbate biomedical consequences. For example, mustard agents and radiation have similar cytotoxic effects and both are immunosuppressive. Clinical and animal studies suggest synergistic effects. Although research on combined injuries is limited, evidence is sufficient to suggest that

Paper presented at the NATO Human Factors and Medicine Panel Research Task Group 099 "Radiation Bioeffects and Countermeasures" meeting, held in Bethesda, Maryland, USA, June 21-23, 2005, and published in AFRRI CD 05-2.

combinations will be more deadly than any injury alone. To be fully prepared for a nuclear or radiological event, it will be important to understand the potential interactions, medical consequences, and treatment options when combined effects are encountered.

1.0 INTRODUCTION

In an accident, a terrorist attack, or an act of war, radiation exposures are likely to be confounded by other injuries, diseases, and toxic chemicals. In this chapter we will review the current status of the research on combined injuries. Although the term "combined injury" has often been used strictly to refer to radiation in combination with traumatic injuries, we will use it to encompass any combined exposure: radiation with a burn, wound, infection, or chemical contact.

Past experiences have shown us that with a nuclear detonation traumatic injuries such as burns and wounds will occur in combination with radiation exposure. Disruption of the public health infrastructure with a nuclear or radiological attack can increase the risk of communicable disease. The source of infection could be endemic opportunistic pathogens or an intentionally dispersed biological warfare agent. Chemical releases from local industrial or storage facilities or by chemical weapons can also complicate radiation injury in an actual event. Trauma, pathogens, and chemicals will all exacerbate the biomedical consequences of irradiation. To be fully prepared for a nuclear or radiological event, it will be important to understand the potential interactions, medical consequences, and treatment options when combined effects are encountered.

2.0 RADIATION AND TRAUMATIC INJURY

Casualty estimates after a nuclear event predict that radiation alone will affect only 15-20% of the injured. Approximately 65-70% of the casualties are expected to receive both radiation and a traumatic injury. These estimates are reflected in the consequences of the bombing of Hiroshima and Nagasaki where 60% to 70% of the radiation victims sustained traumatic injuries in addition to radiation exposure. In the 1986 Chernobyl reactor incident, 10% of the 237 accident victims received both significant radiation doses and burns.

Although the research is limited, several studies demonstrate that traumatic injuries increase the mortality associated with the acute radiation syndrome. In an early study in a canine model, Brooks *et al*. [Brooks 1952]

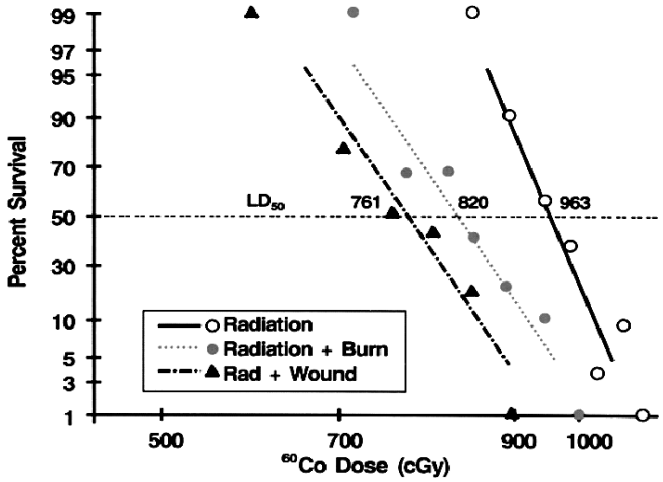

Figure 1: The LD50/30 dose for gamma radiation in mice is decreased when radiation is combined with either a 15% total body surface burn or wound.

combined a thermal burn with radiation. The burn, by itself, was non-lethal. The radiation (1 Gy) caused only 12% mortality. Together they elicited 75% mortality. A similar study in rats [Alpen 1954] combined a 31-35% total body skin area (TBSA) burn that was approximately 50% lethal and sublethal (1 and 2.5 Gy) radiation. With 1 Gy the mortality associated with the burn rose to 65% while 2.5 Gy increased mortality to nearly 100%. At 5.0 Gy (LD_{20}), 75% of the animals died from the combined effects when the burn was non-lethal (16-20% TBSA). A more recent study in mice (Figure 1) demonstrates that burns and wounds shift the radiation dose response curve. Mice were given a range of radiation doses either alone or in combination with a burn or a wound inflicted 24 hours after the radiation. The burn covered approximately 15% of the body surface and by itself caused only 5% lethality. The wound, a transdermal punch of approximately 15% of the body surface, resulted in 5% lethality. The gamma radiation dose that caused 50% lethality decreased from 9.63 Gy with radiation alone to 8.20 Gy with the burn and to 7.61 Gy the wound.

Although the mechanisms underlying the synergism between traumatic injury and radiation exposure are undetermined, increased susceptibility to infection is known to contribute. Trauma alone can effectively depress resistance to infection [Shires 1982]. This is exacerbated by radiation. In combination with sublethal radiation, sublethal burn or sublethal wound trauma synergistically increase translocation of gut bacteria into the bloodstream, leading to greater incidence of death [Mishima 1997, Yan 1995]. Death associated with bacterial translocation occurs 2-4 days after combined injury in a dose-dependent manner [Madonna 1991]. Furthermore, open wounds increase the opportunity for infection. The average healing time for a wound is delayed by radiation exposure. A study in rats [Ran 2004] demonstrated that radiation prolonged the normal 18.3 day recovery by 3.5 days at 4 Gy and 9.5 days at 6 Gy. Both gamma and neutron radiation delay recovery from a wound (Figure 2). Mice in 4 groups of 20 were wounded 1-2 hr after doses of (a) 0 Gy-controls, (b) 2.5 Gy of enriched neutrons (95% neutrons and 5% gamma), (c) 3.5 Gy mixed field (70% neutrons and 30% gamma)

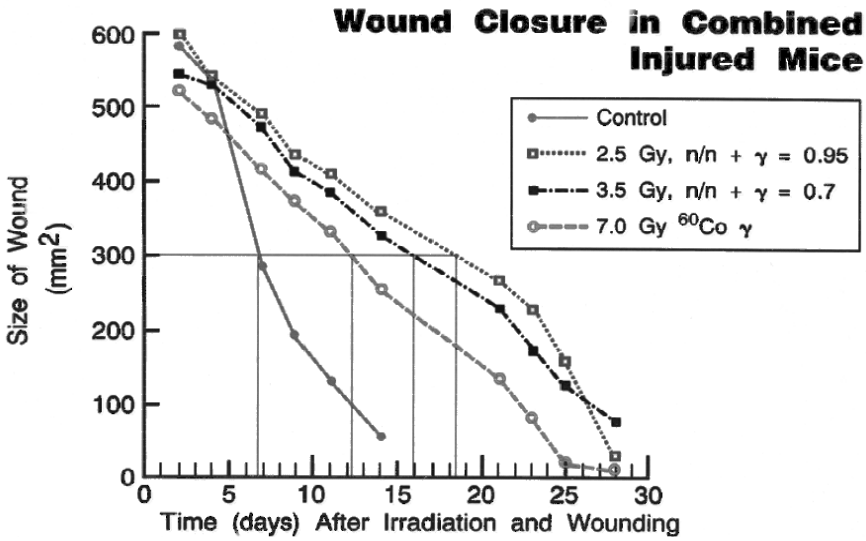

Figure 2: Radiation impairs wound healing.

radiation, or (d) 7.0 Gy gamma. These radiation doses are sublethal; neutron doses were chosen on the basis of an RBE of 2 for the 3.5 Gy mixed field dose and an RBE of about 2.8 for the 2.5 Gy 95% neutron dose as was determined in previous studies. The initial sizes of the wounds were about 600 mm^2 that were aseptically inflicted under methoxyflurane anesthesia. The straight lines indicate a 50% reduction from the 600 mm^2 wound size for all 4 radiation conditions. The graphic lines trace the size of the wound over a 4-week time

frame. Wound sizes less than 100 mm^2 were difficult to determine due to eschar formation. Using the closure of the wound to 100 mm^2, wounds in unirradiated mice closed in about 2 weeks and closed in about 3 weeks for gamma irradiated mice. Wound closure to 100 mm^2 in either neutron irradiated group of mice was not complete until about 4 weeks after irradiation. Although the neutron doses are biologically equivalent to the gamma radiation dose, the data suggest that neutrons induce more damage and/or impair repair processes in the skin epithelial cell-renewal system more that gamma photons.

Combined injuries have implications for clinical care. Antibiotic therapy may need to be started earlier and more aggressively than with radiation alone [Brook 1992]. Closing a skin wound immediately after injury can reduce the synergistic effects. In mice exposed to 5.1 Gy (25% lethality alone) a non-lethal wound 2 days after irradiation increased mortality to 90%. Closing the wound reversed this effect [Cervany 1989]. In contrast, a study on thermal injury in irradiated rats indicated that while a non-lethal burn increased mortality from radiation, excision and closure of the burn 24 hours after radiation did not improve survival [Hirsch 1990]. Because of the interactions of wounds and radiation, the current recommendation is to perform necessary surgical procedures as soon as possible after irradiation, that is within the first 2 or 3 days [Dons 1989, Engelhardt 2001]. Waiting longer can increase mortality. In mice, survivable surgical procedures (laparotomy or splenectomy) increased mortality of 5.1 Gy radiation from 27% to up to 85% depending on time of the procedure. Mortality was up to 60% two days after radiation and maximal on day 8 [Messerschmidt 1966].

3.0 RADIATION AND INFECTIOUS AGENTS

In combination with radiation, morbidity and mortality from exposure to infectious agents will increase significantly. Infectious disease is a likely confounder following a nuclear event that can disrupt public health infrastructure. An infectious agent can be naturally occurring in the environment or it can be intentionally dispersed as a biological warfare agent. Because radiation impairs the immune response and compromises the normal barriers to infection (i.e., the epithelial cell layers of the intestinal tract and lung), an individual becomes more susceptible to pathogens. When radiation injury is combined with exposure to highly infectious pathogens, fewer microbes are needed to establish an infection and the clinical manifestations are more severe, as demonstrated in animal studies.

Irradiated individuals will be more susceptible to endemic bacterial and viral infections. Animal studies demonstrate that radiation increases morbidity and mortality from exposure to pathogens. When sublethally irradi-

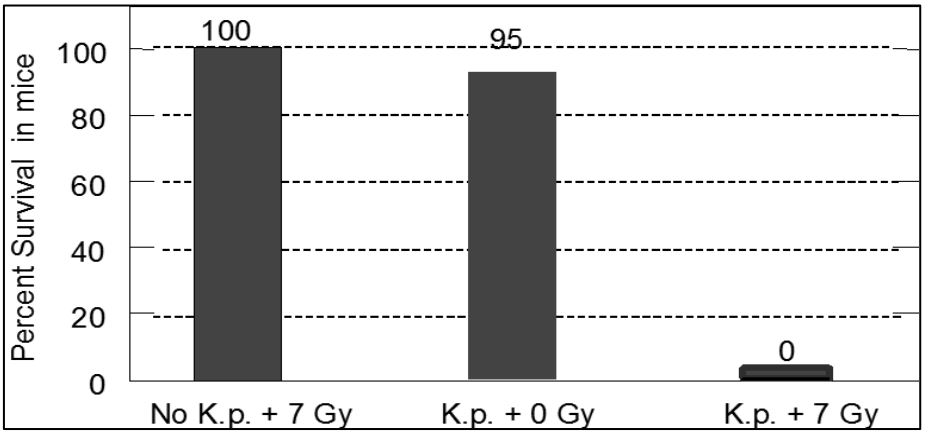

Figure 3: Mortality is increased when radiation exposure is combined with infectious disease. Shown here is the interaction of 7Gy gamma radiation with K. Pneumoniae in mice.

ated mice were exposed to *Klebsiella pneumoniae* (causing 5% mortality in non-irradiated animals), all of the mice died [Ledney 2000, Whitnall 2000] (Figure 3). Even at radiation doses as low as 0.5 Gy, mortality from *K. pneumoniae* was increased. The lethal dose of the bacteria depends on the radiation dose; the higher the radiation dose, the lower the dose of *K. pneumoniae* needed to induce lethality (Figure 4). Susceptibility to infection also varies with time of bacterial challenge relative to time of irradiation. Mortality from *K. pneumoniae* increases within one day of exposure to gamma radiation and stays high for at least two weeks. Similarly, synergistic effects are evident when radiation is combined with exposure to *Shigella sonnei*, a common cause of diarrhea [King 2002, Landauer 2001]. Half of the mice that were colonized with *S. sonnei* four days after a sublethal dose of gamma radiation (7 Gy) died, even though no mice died with the bacterial challenge alone. With a lower radiation dose (3Gy), the mice survived the combined exposure but suffered from enhanced weight loss and performance deficits. Synergistic effects also have been observed with viral infections. Shoemaker *et al.* [Shoemaker 2001] found that mice given a sublethal dose (7 Gy) of gamma radiation

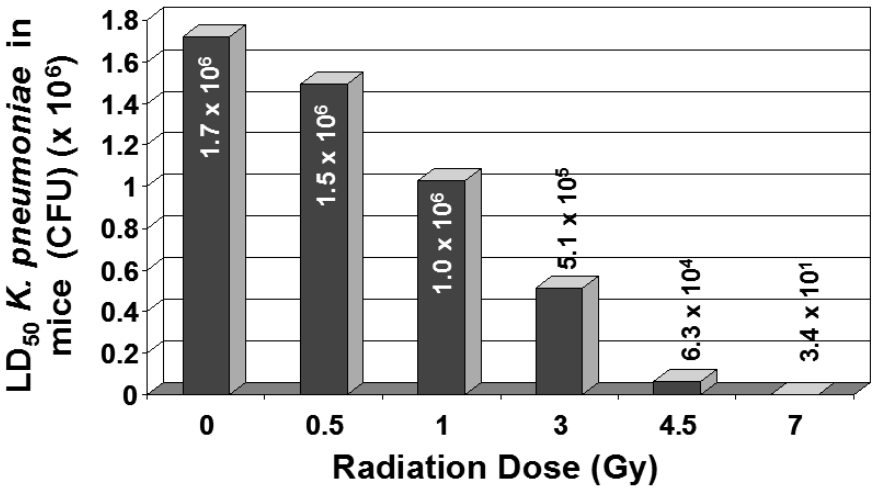

Figure 4: The greater the radiation dose, the fewer the number of pathogenic organisms required to cause morbidity and mortality.

followed two days later by a challenge with Venezuelan Equine Encephalitis (VEE) virus, significantly increased mortality; the number of organisms required to cause death significantly decreased.

Latent infections, such as herpes or scrub typhus, can reactivate after irradiation. Rickettsiae are bacteria transmitted by lice or ticks that can cause typhus. The infection can become dormant and reappear decades later (Brill-Zinsser disease) often in a mild form. When infected animals are irradiated, the illness reappears with fatal consequences. Kelly and Rees [Kelly 1986] infected mice with scrub typhus rickettsiae and one year later gave them gamma radiation. They found that all of the mice presented with an active infection within 2 weeks of irradiation and 90% of them died within a month.

Biological Warfare Agents will synergize with radiation to increase mortality in the population. *Bacillus anthracis* is a bacterial agent that can be used as a biological warfare agent; the spores that form from the bacteria are very stable and easily dispersed. Pulmonary anthrax is usually fatal unless medical intervention begins very quickly after exposure. As with endemic bacterial agents discussed above, studies in mice demonstrate that sublethal doses of gamma radiation significantly increase mortality resulting from exposure to live spores [Knudson 2002]. When mice received sublethal gamma radiation (7 Gy) and challenged four days later with a dose of *B. anthracis* Sterne that alone caused 25% mortality, 92% of the mice died [Elliott 2002a]. Sublethally irradiated mice did not show manifestation of translocation of microorganisms from the intestine to the blood

stream; but many of the animals challenged with radiation and subsequently *B. anthracis* Sterne spores had a polymicrobial infection of both gram-positive and gram-negative bacteria [Brook 2002, Brook 2001, Elliott 2002a, Elliott 2002b]. This finding has significant implications for the antimicrobial treatment of combined exposures.

Vaccine strategies may be compromised by exposure to radiation. Efficacy of immunizations may be impaired by radiation exposure. For example, Hodge *et al.* [Hodge 1969] demonstrated that mice immunized against tularemia after irradiation had a diminished immunity when tested with a challenge of aerosolized, virulent *Francisella tularensis*. In addition, use of live attenuated organisms for immunization may actually cause the manifestation of the disease if given after radiation. Live attenuated vaccine strains of *Bacillus anthracis*, *Francisella tularensis*, and a number of viruses (polio, measles, rubella, mumps, varicella, and yellow fever) have been widely used [Ivins 1990, Knudson 1986, Little 1986]. Hodge *et al.* [Hodge 1969] demonstrated that an immunization dose of the avirulent, live vaccine strain of *Francisella tularensis* in mice became virulent and lethal in mice given low dose-rate gamma radiation. Similarly, inoculation with Venezuelan equine encephalomyelitis virus results in infection rather than immunization in irradiated monkeys [Hilmas 1975].

4.0 RADIATION AND CHEMICAL AGENTS

Although less is known about the physiological interactions of chemicals with radiation, there are sufficient data to suggest that interactions will exacerbate the biomedical consequences. The mustard agents and radiation have similar cytotoxic effects and both are immunosuppressive. In the past, nitrogen mustard and x-irradiation were used in combination to treat various cancers. In one such study, Barrett [Barrett 1960] observed that patients with Hodgkin's disease who received x-irradiation therapy prior to treatment with nitrogen mustard showed a more severe and prolonged bone-marrow depression than those not previously exposed. Barrett [Barrett 1960] further explored this observation in a study using rabbits and demonstrated a synergistic effect of combining gamma irradiation and nitrogen mustard. Rabbits were exposed to whole-body x-irradiation (2.5 Gy) and the bone marrow and blood counts were allowed to recover. A subsequent injection of nitrogen mustard (1.5 mg/kg) showed a significant mortality rate in contrast to the non-irradiated group where no deaths occurred. Interactions of radiation with other chemical agents are less well characterized. However, similar effects of nerve agents and radiation on seizure threshold suggest the possibility of interactions.

5.0 CONCLUSIONS

Although the research on combined injuries has been relatively limited, the evidence is sufficient to suggest that combinations will be more deadly than any injury alone. Combined traumatic injury and irradiation can increase mortality and impair healing. Since radiological injury predisposes casualties to infection, a radiological attack during an outbreak of an endemic disease could cause a significant increase in mortality. A concurrent or subsequent exposure to biological weapons could be devastating. Chemicals, either accidentally or intentionally disseminated, may also exacerbate the biomedical effects of radiation. The medical consequences and the treatment options for combined injuries will need to be fully explored.

6.0 ACKNOWLEDGEMENTS

We thank the members of the NBC Interactions Team at AFRRI, especially the team leader Dr. Gregory

Knudson, and their collaborators for their contributions to the research reported in this manuscript.

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